PATENT COOPERATION TREATY

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From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
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WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	22.02.2000
REPLY DUE	**within 3 month(s)** from the above date of mailing

Applicant's or agent's file reference		
I0277/7004WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/06874	30/03/1999	17/04/1998

International Patent Classification (IPC) or both national classification and IPC
A61K39/395

Applicant
UNIVERSITY OF VERMONT

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 17/08/2000.

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I. Basis of th opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

D scription, pages:

1-95 as originally filed

Claims, No.:

1-142 as originally filed

Drawings, sheets:

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 50, 51, 57, 58, 84-137 and 1-3, 5-9, 13-16, 18-20, 23-26, 29-34, 38, 39, 42-49, 53-56, 139-142 (partially) and 4, 10-12, 17, 21, 22, 27, 28, 35-37, 40, 52, 138 (completely) with respect to industrial applicability,

because:

☒ the said international application, or the said claims Nos. 1-3, 5-9, 13-16, 18-20, 23-26, 29-34, 38, 39, 42-49,

53-56, 139-142 (partially) and 4, 10-12, 17, 21, 22, 27, 28, 35-37, 40, 52, 138 (completely) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 50, 51, 57, 58, 84-137.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	18, 19, 24, 67, 68, 79, 80, 82
Inventive step (IS)	Claims	18-20, 24, 26-28, 67, 68, 79-83
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

s e separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION I

4. Additional observations

This written opinion also takes into consideration pages 1-9 of the Sequence Listing (i.e. information concerning SEQ ID NOs 1 to 13).

SECTION III

Claims 1-3, 5-9, 13-16, 18-20, 23-26, 29-34, 38-39, 42-49, 53-56, 139-142 (partially) and Claims 4, 10-12, 17, 21-22, 27-28, 35-37, 40, 52 and 138 (completely) relate to medical uses considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present Claims 1-3, 5-9, 13-16, 18-20, 23-26, 29-34, 38-39, 42-49, 53-56, 139-142 (partially) and Claims 4, 10-12, 17, 21-22, 27-28, 35-37, 40, 52 and 138 (completely) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION V

2. CITATIONS AND EXPLANATIONS

The attention of the Applicants is drawn to the fact that due to the unclear definition of the subject-matter intended to be claimed/lack of support in the description (Art. 6 PCT) and/or the lack of disclosure (Art. 5 PCT), the present written opinion is based on a **partial International Search Report** (see the further information continued from Form PCT/ISA/210 referring to Box I.2).

2.1 Reference is made to the following document:

D1*: Street, D. et al (1997) Gynecologic Oncology **65**:265-272

*An abstract form of D1 has been cited in the search report. A copy of the complete document is appended hereto

2.2 Novelty and inventive step (Art. 33(2) and (3) PCT)

The present application does not satisfy the criteria set forth in Article 33(2) and (3) PCT because,

a) the subject-matter of Claims 18, 19, 24, 67, 68, 79, 80 and 82 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT)

b) the subject-matter of Claims 18-20, 24, 26-28, 67, 68 and 79-83 does not involve an inventive step (Rule 65(1)(2) PCT).

In the present technical context, the method for inducing lysis of a mammalian cell according to present Claims 18-20, 24 and 26-28 as well as the intended compositions according to Claims 79-83 are anticipated and/or rendered obvious by the disclosure of D1 which teaches a related procedure for inducing/enhancing

the lysis of cervical cancer cells by tumor-specific CTLs wherein the MHC class II HLA-DR inducing agent employed is gamma interferon.

2.3 Claims 67 and 68-73 of the present application are directed to screening kits (i.e. kits of parts) which should meet *per se* the novelty and inventive step requirements of Art. 33(2) and (3) PCT. However, as presently formulated, the constituting elements of the kits are merely characterized by means of non-limiting functional terms. Since the nature of the relevant components is not unambiguously identifiable it cannot be ascertained whether the claimed kits as such relate to novel and inventive subject-matter.

In this regard it is noted that (i) a particular intended use does not limit the scope of a claim directed to a kit to the mentioned use (cf PCT Guidelines, C-III, 4.8 and especially 4.8a) and (ii) the "instructions for determining whether an isolated cell of a subject selectively interacts with the first or second binding compound" of independent Claim 67 and the "instructions for using the cell death marker detection reagent for detecting the presence of a cell death marker" of independent Claim 68 are not regarded as technical features and cannot be used for establishing novelty and/or inventive step over the prior art (cf PCT Guidelines C-III, 2.1 and Rule 6.3(a) PCT).

In view of the foregoing it would nevertheless appear that any known anti-MHC class II HLA-DR antibody when put together with an anti-MHC class II HLA-DP/DQ antibody in a two-container adequate package (as in a generic MHC class II genotyping assay kit) would fall under the scope of present Claim 67. Moreover, in the case of the kit intended in Claim 68 even the commercially available Pharmigen anti-Fas antibody referred to on page 51, lines 9-10 would deprive the claim of novelty and/or inventive step.

2.4 The applicant is requested to file new claims which take account of the above comments (and especially of the deficiencies indicated on Section VIII below).

2.5 The applicant is requested to file amendments by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate.

Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

2.6 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

2.7 Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply rather than be incorporated into the application, Article 34(2)(b) PCT.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

2. The expression "incorporated herein by reference" in respect of prior art documents on page 28 (line 4), page 51 (lines 12-13) and page 94 (lines 24-28) leads to a doubt as to whether the requirements of the description being self-contained are satisfied (see PCT Guidelines C-II, 4.17).

3. The reference on page 94, lines 25-28 to documents which have not been made available to the public before the publication date of the present international

application (i.e. the non-published priority documents pertaining to the present application) is not to be regarded as being part of the disclosure (see PCT Guidelines C-II, 4.18).

4. If the Applicants are aware of registered trade marks used in the description (e.g. "Percoll" mentioned on page 78, line 30, page 91, line 18 and page 93, line 3 or "SuperScript" mentioned on page 93, line 7, etc) they should identify them as such.

SECTION VIII

1. The following generic terms employed in the searched claims either have *per se* no well-recognised meaning or are open to interpretation and leave the reader in doubt as to the meaning of the technical features (i.e. the actual product) to which they refer, thereby rendering the definition of the subject-matter of the indicated claims (and of the claims dependent thereon) unclear, contrary to Article 6 PCT:

"MHC class II HLA-DR ligand" (Claim 79)
"MHC class II HLA-DR inducing agent" (Claim 79)
"MHC class II HLA-DP/DQ ligand (Claims 31, 48 and 75)
"metabolic modifying agent" (Claim 74)
"apoptotic chemotherapeutic agent" (Claims 46, 74 and 142)
"immune recognition molecules" (Claim 44)
"cell death ligand" (Claim 64)
"Fas ligand" (Claim 65)

2. The following products mentioned in the searched claims are defined in terms of non-limiting functional features, e.g. by reference to a desirable characteristic or property:

"MHC class II HLA-DR ligand" (Claims 1, 18 and 39)
"MHC class II HLA-DR inducing agent" (Claims 3, 13 and 18)
"MHC class II HLA-DP/DQ ligand (Claims 14)

"MHC class II HLA-DP/DQ inducing agent" (Claim 16)
"metabolic modifying agent" (Claims 29 and 47)
"apoptotic chemotherapeutic agent" (Claim 29)
"metabolic inhibition agent" (Claim 44)
"Fas binding agent" (Claim 49)

The aforementioned claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. Said claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added, i.e. the actual agents referred to in the supporting description as being, e.g. suitable "MHC class II HLA-DR inducing agents" (see page 23, lines 3-5 and present Claim 80), suitable "MHC class II HLA-DR ligands" (cf page 24, lines 1-4 and Claim 81), suitable "metabolic modifying agents" (cf page 25, lines 13-20 and, in part, Claim 75) etc, should be unambiguously identified in the corresponding claims.

3. In addition to the foregoing, the method of Claim 44 and the intended compositions according to Claims 74-78 and 79-83 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings.

4. The paragraph comprising lines 13-19 on page 14 appears to be misplaced. Moreover it is redundant with the paragraph comprising lines 24-30 on page 12.

   A similar redundancy is found between the paragraph on page 14, lines 9-12 and the paragraph bridging pages 17-18.

5. The statement in the description on page 94, lines 28-32 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

6. In order to avoid any misinterpretation of the subject-matter for which protection is sought, the passages on page 54, lines 24-25 and page 55, lines 3-5 of the description require to be either amended or deleted.

7. The following expressions appear to contain clerical mistakes:

"extracelluar": page 33 (line 25)
"hypersection": page 36 (line 24)
"molecuels": page 46 (line 30)
"petpides": page 46 (line 32)
"isoproteronol": page 76 (line 28), page 77 (line 11), page 78 (line 2)
"separatedaway": page 90 (line 13)
"Intracelluluar": page 90 (line 29)
"in the in the ": page 92 (line 5)
Fig. 1 "apotosis"